DOI:
10.1007/s00134-016-4387-3

It's not breathing through a straw: pediatric extubation readiness tests should not use Pressure Support

Robinder G. Khemani MD, MsCI[1,2], Justin Hotz RCP[1], Rica Morzov RN[1], Rutger C. Flink MS[3], Asvari Kamerkar MD[1], Marie LaFortune MD[5], Gerrard F. Rafferty PhD[4], Patrick A. Ross MD[1,2], Christopher JL Newth MD [1,2]

(1) Children's Hospital Los Angeles, Department of Anesthesiology and Critical Care
(2) University of Southern California Keck School of Medicine, Department of Pediatrics
(3) Med-E Link, Amsterdam, The Netherlands
(4) King's College London, Department of Respiratory Medicine

Work Performed at Children's Hospital Los Angeles

Corresponding Author
Robinder G. Khemani MD
Children's Hospital Los Angeles
4650 Sunset Blvd Mailstop 12
Los Angeles, CA 90027
rkhemani@chla.usc.edu
(323) 361-2376

Sources of Support
National Institutes of Health/NICHD 1K23HL103785
Los Angeles Basin Clinical Translational Science Institute

Word Count: 2707 (without abstract); 2957 (with abstract)

Keywords: Airway Extubation, Work of Breathing, pediatrics, ventilator weaning

Key Points: By performing direct measures of patient effort of breathing before and after extubation on over 400 mechanically ventilated children, we have found that patient effort of breathing on CPAP of 5cm$H_2$0 alone provides a good estimate of post-extubation effort. Regardless of the endotracheal tube size, pressure support should not be added to CPAP for extubation readiness testing because it results in significant under-estimation of post-extubation effort of breathing.

Social Network: Regardless of endotracheal tube size, PS during ERTs significantly under-estimates post-extubation effort of breathing.

Abstract

Purpose: Pressure Support (PS) is often used for extubation readiness testing (ERT), to overcome perceived imposed work of breathing from endotracheal tubes (ETT). We sought to determine whether effort of breathing on Continuous Positive Airway Pressure (CPAP) of 5cmH_2O is higher than post-extubation effort, and if this is confounded by ETT size or post-extubation noninvasive respiratory support (NIV).

Methods: Prospective trial in intubated children. Using esophageal manometry we compared effort of breathing with Pressure.Rate Product (PRP) under 4 conditions: PS 10/5 cmH_2O (PS), CPAP 5 cmH_2O (CPAP), and spontaneous breathing 5 and 60 minutes post-extubation. Subgroup analysis excluded post-extubation upper airway obstruction (UAO) and stratified by ETT size and post-extubation NIV.

Results: We included 409 children. Median PRP on PS was lower than CPAP which was lower than post extubation: PS 100 (IQR 60,175), CPAP 200 (120,300), post-extubation 5min 300 (150,500), 60min 255 (175,400) (all $p<0.001$). Excluding 107 patients with post-extubation UAO (where PRP after extubation is expected to be higher), PS still under-estimated post-extubation effort by 126-147%, and CPAP underestimated post-extubation effort by 17-25%. For all ETT subgroups: ≤ 3.5 mmID (n=152), 4-4.5 mmID (n=102), and ≥ 5.0 mmID (n=48) PRP on PS was lower than CPAP and post-extubation (all $p<0.0001$), while CPAP PRP was not different than post-extubation (all $p>0.05$). For patients on NIV, PRP on PS was lower than CPAP and post-extubation ($p<0.0001$), while CPAP PRP was not different than post-extubation (n=81).

Conclusions: Regardless of endotracheal tube size, PS during ERTs significantly under-estimates post-extubation effort of breathing.

Word Count: 250

Introduction

Critical care practitioners commonly add Pressure Support (PS) during extubation readiness tests (ERT) to overcome perceived imposed resistance of the endotracheal tube (ETT) [1-3]. A recent survey of pediatric critical care practitioners identified that 94% add PS to Positive End Expiratory Pressure (PEEP) when performing ERTs [4]. There is a reluctance to wean patients to Continuous Positive Airway Pressure (CPAP) alone (without PS), or to T-piece ventilation, hypothesizing patients work harder to breathe on CPAP than they will extubated because of small ETT diameters (smaller than the trachea) and imposed resistance from ventilator circuits [2]. This perception is amplified because the internal diameter of the ETT is often reduced by secretions or biofilm, further increasing airway resistance [5-7].

However, resistance through a tube depends on flow [8]. Previous in vitro work has demonstrated that resistance of the smallest ETTs is higher when matched for flow (i.e. 15 L/min through 3.5 ETT has higher resistance than 15 L/min through 6.0 ETT), but children with 3.5 ETT generally breathe at lower flow rates than those who have 6.0 ETT [9]. Several studies demonstrate that PS or Automatic endotracheal Tube Compensation (ATC) overcome imposed resistance from the ETT or ventilator circuits [3, 5, 10-13]. However, these studies do not factor in the resistance of the natural airway, and have not routinely measured the difference between effort of breathing before and after extubation. There are limited controlled data demonstrating that ERTs using ATC or PS result in higher rates of successful extubation compared to CPAP or T-Piece in adults [14-16], and no pediatric data. The increasing use of non-invasive respiratory support (NIV) after extubation has complicated this picture, as it is unclear if using NIV after extubation affords patients to be extubated from higher PS because of a belief that NIV can further lower effort of breathing after extubation.

While we have previously demonstrated that PS underestimates post-extubation effort, our findings were limited by small sample size, inability to control for post-extubation Upper Airway Obstruction (UAO), and no subgroup analysis based on ETT size or NIV [17]. We hypothesized that effort of breathing on CPAP of 5cmH_2O was not higher than post-extubation values, and that using PS prior to extubation would significantly underestimate post-extubation effort. We tested this hypothesis by comparing effort of breathing for children before extubation on PS with PEEP and CPAP alone to effort of breathing post-extubation. We, a-priori, sought to control for post-extubation UAO and stratify by size of ETT and use of NIV after extubation. Some of these findings have previously been published in abstract form [18].

Methods

We screened intubated children in the pediatric or cardiothoracic intensive care units at Children's Hospital Los Angeles from July 2012-April 2015. Inclusion criteria: >37 weeks gestational age - 18 years, intubated ≥ 12 hours with planned extubation from 7 am to 5 pm Monday-Friday. Exclusion criteria: contraindication to an esophageal catheter or Respiratory Inductance Plethysmography (RIP) bands. Informed consent was obtained from the parent/guardian, with approval from the Institutional Review Board and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of

Helsinki and its later amendments. This was a planned secondary analysis to a study on post-extubation UAO, which contains further details about methods [19].

Study Protocol

Prior to extubation, each child received an esophageal balloon catheter and had RIP bands calibrated under tidal breathing on CPAP of 5 cmH_2O [20, 21]. A self-calibrating pneumotachometer was used prior to extubation to measure peak inspiratory flow during tidal breathing.

Patients were studied under 4 conditions: Pressure Support 10/PEEP 5 cmH_2O (PS), CPAP 5 cmH_2O (CPAP), and spontaneous breathing, 5 (5min) and 60 (60min) minutes after extubation. We recorded data during 5 minutes of steady state breathing on each condition, and calculated the median Pressure.Rate Product (PRP = peak-to-trough change in esophageal pressure (cmH_2O) * respiratory rate (breaths per minute)) on each condition. PRP is a surrogate for effort of breathing [22-25], and unlike work of breathing (calculated from the pressure-volume curve) PRP does not need to be sub-divided into patient versus ventilator effort. All of the PRP is attributable to the patient, making it appropriate for comparing patient effort on and off mechanical ventilation. While Pressure Time Product can also be used, PRP is easier to calculate and in our experience more robust against artifact, particularly in young children.

If the patient was initiated on non-invasive respiratory support (NIV) within 60 minutes of extubation (High Flow Humidified Nasal Cannula, Nasal Intermittent Mandatory Ventilation, CPAP or BIPAP), additional measurements were obtained 15-20 minutes after NIV initiation.

One of two ventilators was used for PS and CPAP: SERVO-I ® (MAQUET) and AVEA® (Carefusion). Automatic endotracheal tube compensation is available on the AVEA®, but was off during measurements.

UAO (either subglottic or supraglottic) was labeled as present after extubation when there was inspiratory flow limitation on the plot of flow from calibrated RIP and esophageal pressure, as previously published using this cohort [19]. A priori subgroup analysis was planned excluding children with post-exutbation UAO, stratifying by ETT size. Additional subgroup analysis was planned for those on NIV within 60 minutes of extubation. Average peak inspiratory flow (L/min) was measured from spirometry during 2-3 minutes of steady state breathing on CPAP of 5 cmH_2O. Peak inspiratory resistance (cmH_20/L/sec) was calculated using the patient's ETT size and measured peak inspiratory flow, using formulae derived from in-vitro studies [9].

<u>Analysis</u>

We hypothesized that effort of breathing on CPAP of 5cmH_2O was not higher than post-extubation effort, and attempting to "overcome endotracheal tube resistance" with PS would underestimate post-extubation effort of breathing. Secondary objectives were to determine whether this relationship was confounded by size of ETT, or use of post-extubation NIV. For all subgroup analyses, we excluded patients with post-extubation UAO because post-extubation PRP is expected to be significantly higher than pre-extubation PRP, and including these patients may bias results in favor of our hypothesis. Three ranges of ETT sizes were used for subgroup analysis (≤ 3.5 mmID, 4.0-4.5 mmID, and ≥ 5.0 mmID), ensuring sufficient patients per group for analysis. Separate subgroup analysis was performed for patients on NIV within 1 hour of extubation, comparing pre-extubation PRP with PRP 15-20 minutes after NIV initiation. Descriptive statistics are reported using median (interquartile range) or number (percent). Box and whisker plots demonstrate differences in PRP under the 4 study conditions. For analysis, PRP was log transformed for repeated measures ANOVA with Scheffe's test for post-hoc multiple comparisons. Statistical analysis was performed in Statistica 10 (Dell, Tulsa, Oklahoma) and Stata 10 (Stata-Corp, College Station, Texas).

Results

A total of 1159 patients were eligible and 409 were included, with a median age of 5 months (IQR 1, 16) and 55% male. The most common reasons eligible patients were not enrolled were: (a) parents unavailable for consent and (b) extubation during a night or weekend when the study team was unavailable. Demographics and reasons for non-enrollment have been previously published [19]. Approximately half were intubated for cardiac surgery. Median length of mechanical ventilation was 4.1 days (IQR 1.4, 8.0 days). Thirty-four patients were re-intubated (8.3%), and 107 (26%) had post-extubation UAO (subglottic or supraglottic) within 1 hour of extubation. One hundred and seven (26%) children were on NIV within 1 hour of extubation (mostly HFNC).

Resistance as a function of flow and endotracheal tube size

For the entire cohort, 209 (51%) had an ETT ≤ 3.5 mmID, 143 (35%) were 4.0 or 4.5 mmID, and 57 (14%) were ≥ 5.0 mmID. Peak inspiratory flow increased as ETT size increased (Figure 1). While peak inspiratory resistance was higher for smaller ETTs, median peak inspiratory resistance was lower in intubated children compared to expected values while extubated, even with a 3.0 ETT on CPAP of 5 cmH_2O [26-29] (Figure 1). The flow rates used by most infants and children while intubated on CPAP are in a range in which significant increases in resistance are not expected (Figure 2).

Effort of breathing before and after extubation

For the entire cohort (n=409), median PRP was 100 (IQR 60,175) on PS 10/5 cmH_2O, 200 (IQR 120,300) on CPAP of 5 cmH_2O, 300 (IQR 150,500) 5 minutes after extubation, and 255 (IQR 175,400) 60 minutes after extubation (Figure 3). PS PRP was lower than CPAP and post extubation PRP (multiple comparisons $p<0.0001$) and CPAP PRP was lower than post extubation PRP (multiple comparisons $p< 0.0001$). Restricting the analysis to patients without post-extubation UAO (n=302), there were similar trends in median PRP values as a function of level of support, with slightly lower values for the post-extubation PRP (Figure 4). Again, PS PRP was lower than CPAP and post extubation PRP (multiple comparisons $p<0.0001$) and CPAP PRP was lower than post extubation PRP (multiple comparisons $p< 0.02$).

Excluding patients with UAO, 5 minutes after extubation individual patient's PRP was a median 25% (IQR -5%, 72%) higher than CPAP values and 147% (67, 267%) higher than PS values. By 60 minutes after extubation, individual patient's PRP remained a median 17% (-20%, 60%) higher than CPAP values, and 126% (40%, 233%) higher than PS values.

Subgroup Analysis: Endotracheal tube size and NIV

We subsequently sub-grouped children without UAO (n=302) by size of ETT. The patterns were the same for endotracheal tube size groupings of ≤ 3.5 mmID (n=152, Figure 5a), 4-4.5 mmID (n=102, Figure 5b), and ≥ 5.0 mmID (n=48, Figure 5c). Regardless of ETT subgrouping, PS PRP was less than CPAP and post-extubation PRP (all multiple comparisons $p < 0.01$), while within each ETT subgroup CPAP PRP was similar to post extubation PRP (all multiple comparisons $p > 0.05$).

When examining the cohort of 107 children who were placed on NIV within 1 hour of extubation, 26 had post-extubation UAO. In the remaining 81 patients (2 BiPAP, 74 HFNC, 5 Nasal IMV) the median PRP on PS 135 (IQR 90,220) was significantly lower than PRP on either CPAP 270 (200,400) prior to extubation or post-extubation on NIV 320, (220, 420) (multiple comparisons $p < 0.0001$). However there was no difference in PRP on CPAP prior to extubation and PRP post-extubation on NIV (multiple comparisons $p = 0.8$).

Discussion

We have demonstrated that using PS during ERTs significantly under-estimates post-extubation effort of breathing in children, regardless of ETT size or use of non-invasive respiratory support (mostly HFNC) after extubation. Effort of breathing on CPAP of 5 cmH_2O may still under-estimate post-extubation effort, although on average it is 15-25% lower than post-extubation, and appears similar to effort of breathing on NIV after extubation. In other words, if the patient cannot tolerate CPAP 5 cmH_2O alone prior to extubation, they are unlikely to do well after extubation, even with NIV. While inspiratory resistance increases as ETT size decreases, prior to extubation children are breathing with flow rates where predicted inspiratory resistance is actually below extubated values [26-29]. Therefore, we have found no evidence to support adding any amount of PS to "reduce imposed work of breathing" during ERTs in children, regardless of the ETT size.

Extubation failure rates are generally low in children, on average 8% [30]. Moreover, nearly half of extubation failures are from post-extubation UAO [19, 20, 30], which may be difficult to predict during standard ERTs [31-33]. With < 5% of patients failing extubation from causes other than UAO, it is difficult to demonstrate that one mode of ERT results in lower re-intubation rates. This low extubation failure rate has perhaps lulled pediatric practitioners into a sense of security about using PS. If < 5% of patients fail extubation when PS is used, why should we be more restrictive about whom we extubate by mandating ERTs be done on CPAP.

Perhaps our extubation failure rates are too low. This is supported by the > 50% success rate of unplanned extubations in pediatrics [30], highlighting many patients can be extubated well before we recognize they are ready. Daily SBTs have been advocated as part routine practice, but fewer than 25% of pediatric practitioners use them [4]. Perhaps patients can be successfully extubated sooner [2, 34] if we routinely perform SBTs earlier in the mechanical ventilation course [8]. Once we start doing this, based on the physiologic data presented in this paper, it is possible we would have higher extubation failure rates if effort of breathing on PS is used during ERTs.

From our data, we believe CPAP of 5 cmH_2O alone is sufficient for ERTs in most children, given effort of breathing after extubation is generally 15-25% higher than values on CPAP of 5 cmH_2O, and is similar to what is provided with NIV post-extubation. While our previous work did not find major differences in effort of breathing between CPAP and T-piece [17], some patients may warrant further reductions to T-piece ventilation, or warrant longer SBTs, such as those with neuromuscular disease. In addition, some patients warrant CPAP > 5 cmH_20 during SBTs, such as children with obesity. When extubated, these children may use other mechanisms to maintain normal trans-pulmonary pressures at end exhalation, and weaning to CPAP of 5 cmH_2O may result in more alveolar collapse then they would have extubated. Ultimately, the duration of the SBT and level of end expiratory pressure (CPAP or T-piece) should be determined by an experienced provider mindful of the expected pathophysiology of the patient. However, we believe our data support PS should not be added to this end expiratory pressure, even when extubation is planned to HFNC, as CPAP prior to extubation still best estimates post-extubation effort. Because of limited number of patients on non-invasive CPAP or BiPAP post extubation, it is unclear if the same holds when extubating to these modes of non-invasive positive pressure.

There are several limitations to our study, despite its prospective nature. First, it is single institution, although we believe generalizability is high given this is a physiologic study. Second, we obtained a convenience sample because we did not study patients on nights or weekends, or patients who did not consent. This may introduce a selection bias on types of patients enrolled. Moreover, these patients were intubated for many reasons (cardiac surgery, pulmonary disease etc…) and independent of work of breathing, ERTs may use different criteria based on patient factors. Third, we excluded patients with post-extubation UAO using an "objective" UAO parameter we have previously reported, but there still may be some imprecision in labelling patients with UAO. Fourth, we had only 3 patients with size 2.5 mmID ETTs, precluding subgroup analysis. Our findings may not generalize to premature or small for gestational age children with 2.5 mmID ETT. Fifth, NIV was mostly HFNC, and the results may differ with mask CPAP or BiPAP. Unfortunately, this represents institutional preference for HFNC as we had only 2 patients without UAO on BiPAP within 60 minutes of extubation. Sixth, our illustrative calculations of airway resistance were based on measured patient flow with bench models of ETTs to determine resistance. Actual resistance in vivo could be lower because of less heat loss when connected to the patient versus exposed to atmosphere, or higher if the internal diameter of the ETT is reduced from secretions or biofilm. Unfortunately we did not measure resistance as part of the study, and it is difficult to attribute measured resistances in vivo to just the upper airway. To that end, there are few published norms for upper airway resistance in spontaneously breathing infants and children, and there are differences between peak resistance (used in our study) and mean resistance. This makes precise definitions of normal values of upper airway resistance complicated [26, 27, 29]. Nevertheless, this will not influence the effort of breathing results, which clearly illustrate that effort of breathing on CPAP is lower than when extubated for most patients, regardless of resistance. Seventh, we used two different ventilators which may deliver CPAP and PS in different ways. Finally, this study did not examine re-intubation because of the relatively few cases of re-intubation from causes other than UAO.

In conclusion, Pressure Support should not be added to CPAP to overcome “imposed work of breathing” from the ETT during SBTs or ERTs in children, regardless of the size of the ETT. Using

Pressure Support greatly under-estimates post-extubation effort of breathing (125-150% under-estimation), while effort of breathing on CPAP of $5cmH_2O$ alone may still under-estimate post-extubation effort of breathing by 15-25%.

Acknowledgements

The authors would like to thank Aaron Clute, Ed Guerrero, Edwin Khathetourian, and Cary Sodetani RCPs for their assistance with the study protocol; Anoopindar Bhalla, Sarah Rubin, and Timothy Deakers for their assistance with consents; Jeffery Terry and Paul Vee for administrative support, and all the bedside providers in the CHLA PICU and CTICU for their participation and support.

Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Figure Legends

Figure 1: Peak inspiratory flow (dotted) (L/min) and Peak Inspiratory resistance (solid) (cmH$_2$0/L/sec) as a function of endotracheal tube size. Note, 2.5 endotracheal tube was excluded from graph because there were only 3 measurements. 6.0 endotracheal tube includes all those with ETT $\geq$ 6.0 mmID. While resistance is nearly 3 fold higher for 3.0 ETT compared to 6.0 ETT, these values are lower than peak resistance with a natural airway.

Figure 2: Range of peak resistance (cmH$_2$0/L/sec) expected based on actual patient peak inspiratory flow (L/min), superimposed on bench model of ETT resistance from Manczur et al. Note that for patients with small endotracheal tubes, flow is lower, predicting resistances that are still lower than expected with a natural airway.

Figure 3: PRP as a function of pre-extubation support (PS= Pressure Support of 10/PEEP of 5 cmH$_2$O), CPAP (Continuous Positive Airway Pressure=5 cmH$_2$O), and spontaneously breathing 5 and 60 minutes post extubation, for the entire cohort of 409 children. All PRP values were significantly different than one another, with PRP PS < PRP CPAP < PRP post-extubation (log transformed PRP, ANOVA $p<0.0001$, multiple comparisons all p0.0001).

Figure 4: PRP as a function of pre-extubation support (PS= Pressure Support of 10/PEEP of 5 cmH$_2$O), CPAP (Continuous Positive Airway Pressure=5 cmH$_2$O), and spontaneously breathing 5 and 60 minutes post extubation, excluding the 107 patients with post-extubation UAO. All PRP

values were significantly different than one another with PRP PS < PRP CPAP < PRP post-extubation (log transformed PRP, ANOVA $p<0.0001$, multiple comparisons all $p< 0.02$).

Figure 5 a-c: PRP as a function of pre-extubation support (PS= Pressure Support of 10/PEEP of 5 cmH_2O), CPAP (Continuous Positive Airway Pressure=5 cmH_2O), and spontaneously breathing 5 and 60 minutes post extubation, excluding the 107 patients with post-extubation UAO, stratified by endotracheal tube size. The patterns were the same for endotracheal tube size groupings of ≤ 3.5 mmID (n=152, a, top left), 4-4.5 mmID (n=102, b, bottom left), and ≥ 5.0 mmID (n=48, c, top right). Regardless of endotracheal tube subgrouping, PS PRP was less than CPAP PRP (log transformed PRP, ANOVA $p<0.0001$, multiple comparisons all $p< 0.01$). CPAP PRP was similar to post-extubation PRP ($p>0.05$).

References

1. Curley MA, Wypij D, Watson RS, Grant MJ, Asaro LS, Cheifetz IM, Dodson BL, Franck LS, Gedeit RG, Angus DC, Matthay MA, RESTORE, Network P, (2015) Protocolized Sedation vs. Usual Care in Pediatric Patients Mechanically Ventialted for Acute Respiratory Failure. Jama 313: 379-389
2. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, Luckett PM, Forbes P, Lilley M, Thompson J, Cheifetz IM, Hibberd P, Wetzel R, Cox PN, Arnold JH, Pediatric Acute Lung I, Sepsis Investigators N, (2002) Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. Jama 288: 2561-2568
3. Fiastro JF, Habib MP, Quan SF, (1988) Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. Chest 93: 499-505
4. Mhanna MJ, Anderson IM, Iyer NP, Baumann A, (2014) The use of extubation readiness parameters: a survey of pediatric critical care physicians. Respir Care 59: 334-339
5. Fujino Y, Uchiyama A, Mashimo T, Nishimura M, (2003) Spontaneously breathing lung model comparison of work of breathing between automatic tube compensation and pressure support. Respir Care 48: 38-45
6. Straus C, Louis B, Isabey D, Lemaire F, Harf A, Brochard L, (1998) Contribution of the endotracheal tube and the upper airway to breathing workload. Am J Respir Crit Care Med 157: 23-30
7. Wilson AM, Gray DM, Thomas JG, (2009) Increases in endotracheal tube resistance are unpredictable relative to duration of intubation. Chest 136: 1006-1013
8. Newth CJ, Venkataraman S, Willson DF, Meert KL, Harrison R, Dean JM, Pollack M, Zimmerman J, Anand KJ, Carcillo JA, Nicholson CE, Eunice Shriver Kennedy National Institute of Child H, Human Development Collaborative Pediatric Critical Care Research N, (2009) Weaning and extubation readiness in pediatric patients. Pediatr Crit Care Med 10: 1-11
9. Manczur T, Greenough A, Nicholson GP, Rafferty GF, (2000) Resistance of pediatric and neonatal endotracheal tubes: influence of flow rate, size, and shape. Crit Care Med 28: 1595-1598
10. Oto J, Imanaka H, Nakataki E, Ono R, Nishimura M, (2012) Potential inadequacy of automatic tube compensation to decrease inspiratory work load after at least 48 hours of endotracheal tube use in the clinical setting. Respir Care 57: 697-703
11. Fabry B, Haberthur C, Zappe D, Guttmann J, Kuhlen R, Stocker R, (1997) Breathing pattern and additional work of breathing in spontaneously breathing patients with different ventilatory demands during inspiratory pressure support and automatic tube compensation. Intensive Care Med 23: 545-552
12. Haberthur C, Elsasser S, Eberhard L, Stocker R, Guttmann J, (2000) Total versus tube-related additional work of breathing in ventilator-dependent patients. Acta Anaesthesiol Scand 44: 749-757
13. Aguilar G, Jover JL, Soro M, Belda FJ, Garcia-Raimundo M, Maruenda A, (2005) Additional work of breathing and breathing patterns in spontaneously breathing patients during pressure support ventilation, automatic tube compensation and amplified spontaneous pattern breathing. Eur J Anaesthesiol 22: 312-314

14. Cohen J, Shapiro M, Grozovski E, Fox B, Lev S, Singer P, (2009) Prediction of extubation outcome: a randomised, controlled trial with automatic tube compensation vs. pressure support ventilation. Crit Care 13: R21
15. Cohen JD, Shapiro M, Grozovski E, Lev S, Fisher H, Singer P, (2006) Extubation outcome following a spontaneous breathing trial with automatic tube compensation versus continuous positive airway pressure. Crit Care Med 34: 682-686
16. Haberthur C, Mols G, Elsasser S, Bingisser R, Stocker R, Guttmann J, (2002) Extubation after breathing trials with automatic tube compensation, T-tube, or pressure support ventilation. Acta Anaesthesiol Scand 46: 973-979
17. Willis BC, Graham AS, Yoon E, Wetzel RC, Newth CJL, (2005) Pressure-rate products and phase angles in children on minimal support ventilation and after extubation. Intensive Care Med 31: 1700-1705
18. Khemani R, Flink R, Morzov R, Ross P, Newth C, (2013) Its not like breathing through a straw: Effort of breathing on CPAP most accurately estimates post-extubation effort in children. American Journal of Respiratory and Critical Care Medicine suppl 2013.187.1: A3682
19. Khemani RG, Hotz J, Morzov R, Flink R, Kamerkar A, Ross PA, Newth CJ, (2016) Evaluating Risk Factors for Pediatric Post-extubation Upper Airway Obstruction Using a Physiology-based Tool. Am J Respir Crit Care Med 193: 198-209
20. Khemani R, Flink R, Hotz J, Ross P, Ghuman A, Newth CJ, (2015) Respiratory inductance plethysmography calibration for pediatric upper airway obstruction: an animal model. Pediatr Res 77: 75-83
21. Sackner MA, Watson H, Belsito AS, Feinerman D, Suarez M, Gonzalez G, Bizousky F, Krieger B, (1989) Calibration of respiratory inductive plethysmograph during natural breathing. J Appl Physiol 66: 410-420
22. Ross PA, Hammer J, Khemani R, Klein M, Newth CJ, Ross PA, Hammer J, Khemani R, Klein M, Newth CJL, (2010) Pressure-rate product and phase angle as measures of acute inspiratory upper airway obstruction in rhesus monkeys. Pediatr Pulmonol 45: 639-644
23. Diblasi RM, Zignego JC, Tang DM, Hildebrandt J, Smith CV, Hansen TN, Richardson CP, (2010) Noninvasive respiratory support of juvenile rabbits by high-amplitude bubble continuous positive airway pressure. Pediatr Res 67: 624-629
24. Argent AC, Hatherill M, Newth CJ, Klein M, (2008) The effect of epinephrine by nebulization on measures of airway obstruction in patients with acute severe croup. Intensive Care Med 34: 138-147
25. Argent AC, Newth CJ, Klein M, (2008) The mechanics of breathing in children with acute severe croup. Intensive Care Med 34: 324-332
26. Davis S, Gappa M, Rosenfeld M (2005) Respiratory Mechanics. In: Hammer J, Eber E (eds) Paediatric Pulmonary Function Testing. Karger, Basel, pp. 30
27. Masters IB, Seidenberg J, Hudson I, Phelan PD, Olinsky A, (1987) Longitudinal study of lung mechanics in normal infants. Pediatr Pulmonol 3: 3-7
28. Hammer J, Patel N, Newth CJ, (2003) Effect of forced deflation maneuvers upon measurements of respiratory mechanics in ventilated infants. Intensive Care Med 29: 2004-2008
29. Hammer J, Numa A, Newth CJ, (1997) Acute respiratory distress syndrome caused by respiratory syncytial virus. Pediatr Pulmonol 23: 176-183
30. Kurachek SC, Newth CJ, Quasney MW, Rice T, Sachdeva RC, Patel NR, Takano J, Easterling L, Scanlon M, Musa N, Brilli RJ, Wells D, Park GS, Penfil S, Bysani KG, Nares MA, Lowrie L, Billow M, Chiochetti E, Lindgren B, (2003) Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. Crit Care Med 31: 2657-2664

31. Wratney AT, Benjamin DK, Jr., Slonim AD, He J, Hamel DS, Cheifetz IM, (2008) The endotracheal tube air leak test does not predict extubation outcome in critically ill pediatric patients. Pediatr Crit Care Med 9: 490-496
32. Mhanna MJ, Zamel YB, Tichy CM, Super DM, (2002) The "air leak" test around the endotracheal tube, as a predictor of postextubation stridor, is age dependent in children. Crit Care Med 30: 2639-2643
33. Khemani R, Hotz J, Morzov R, Kamerkar A, Flink R, PA R, Newth CJ, (2015) Risk factors for pediatric post-extubation upper airway obstruction. American J Respir Crit Care Med 191: A4068
34. Jouvet PA, Payen V, Gauvin F, Emeriaud G, Lacroix J, (2013) Weaning children from mechanical ventilation with a computer-driven protocol: a pilot trial. Intensive Care Med 39: 919-925

Figure 1 Click here to download Figure Figure1.tif

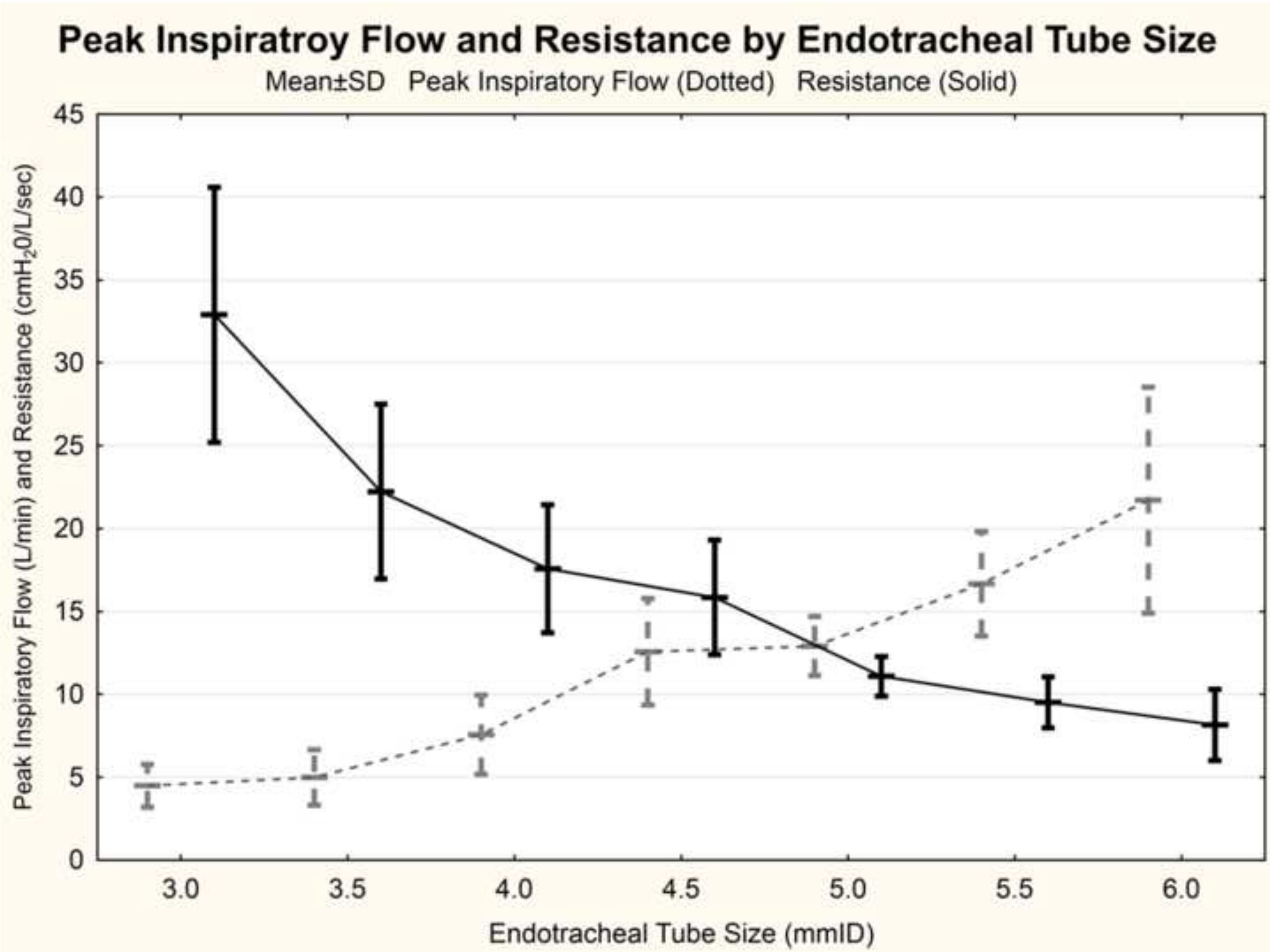

Figure 2 Click here to download Figure Figure2.tif

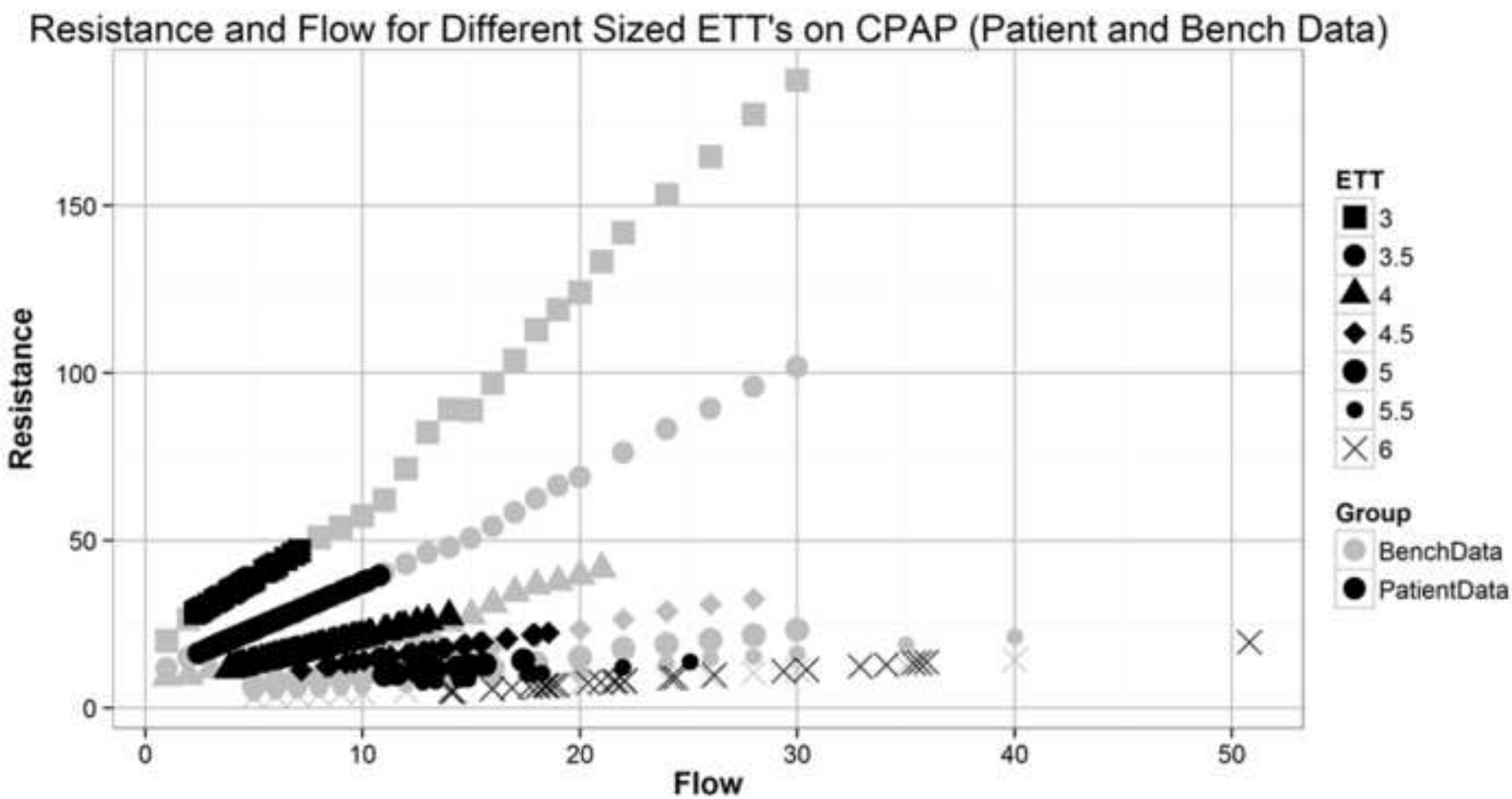

Figure 3

Click here to download Figure Figure3.tif

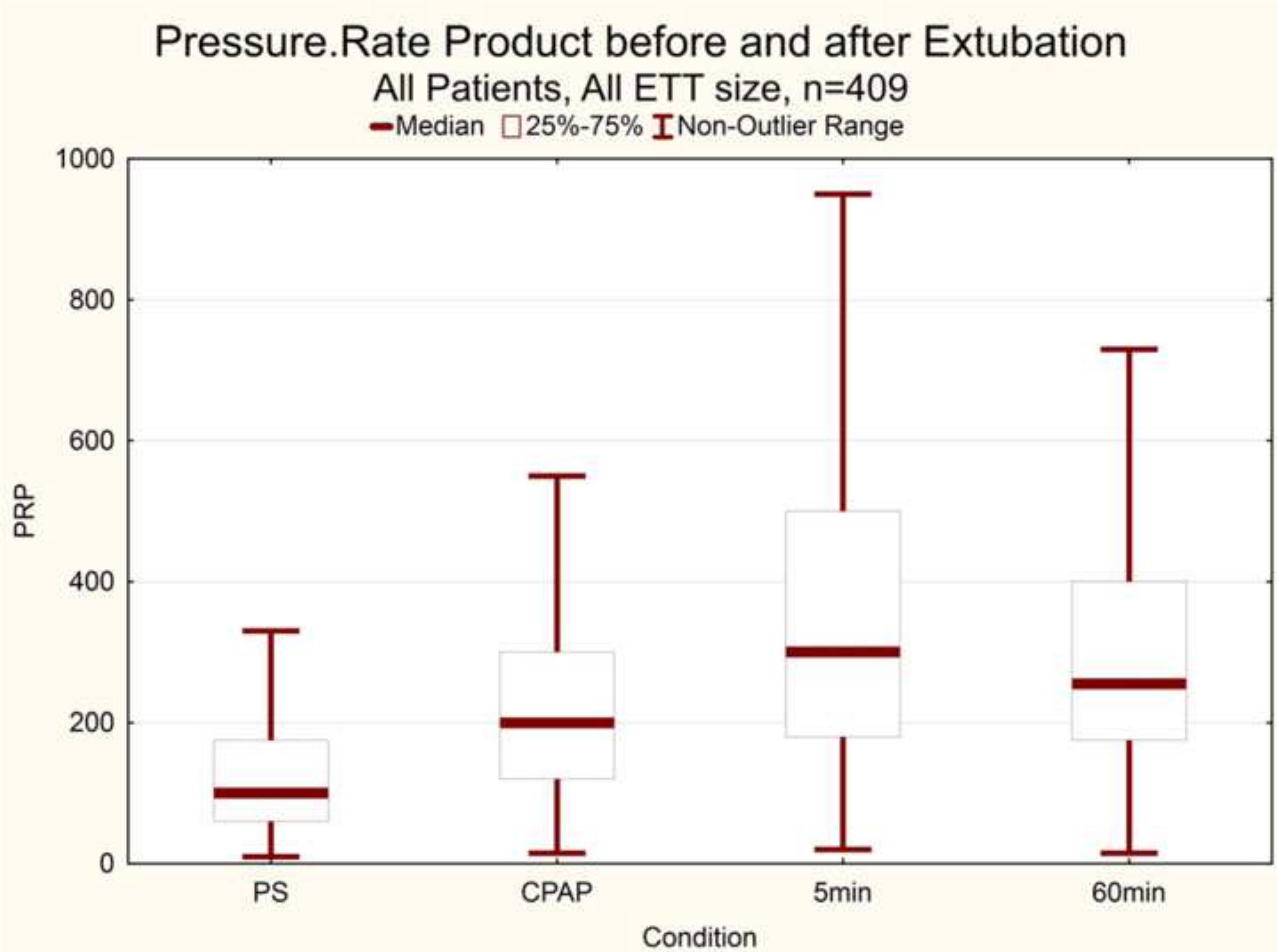

Figure 4 Click here to download Figure Figure4.tif

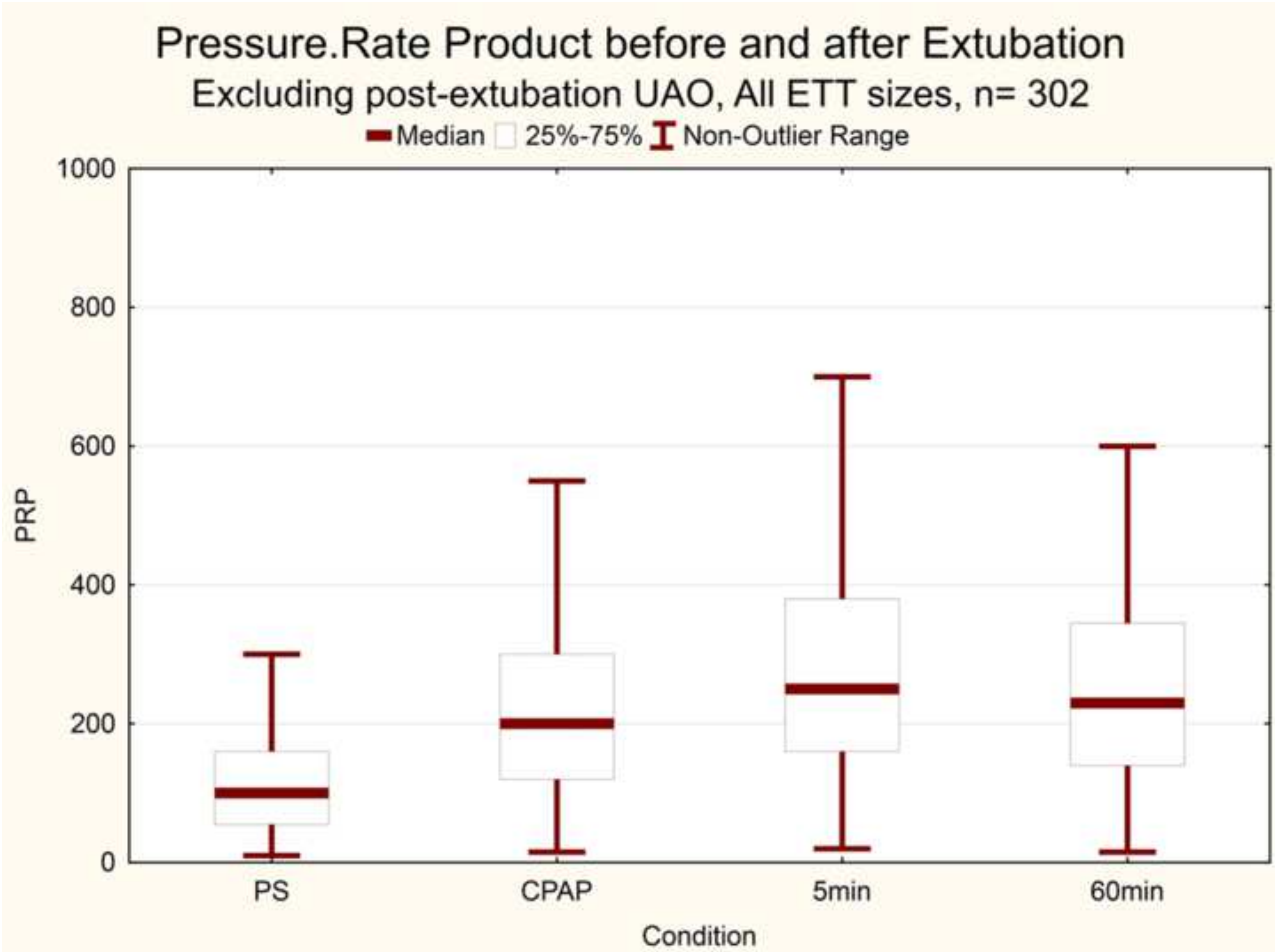

Figure 5

Click here to download Figure Figure5.tif